In re Application of: Levitzki et al
Serial No.: 10/715,547
Filed: November 19, 2003
Office Action Mailing Date: April16, 2007

Examiner: Tamthom N. Truong
Group Art Unit: 1624
Attorney Docket: 27148

REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-34 are in this case. Claims 4, 5, 12-27 and 32-34 have been withdrawn from further consideration as being drawn to a non-elected invention. Claims 1-3, 6-11 and 28-31 have been examined on the merits. Claims 1-3, 6-11 and 28-31 have been rejected. Claims 6-8 have now been canceled. Claims 1-3, 9, 28 and 30 have now been amended.

Amendments to the Specification

In view of the Examiner's remarks under 35 U.S.C. 112, second paragraph rejections below, Applicant has chosen to amend the specification, so as to correct some typographical errors.

Specifically, on page 6, line 2 (paragraph [0012]), the word "provided" has been replaced by the word "provide"; on page 7, line 6 (paragraph [0017]) and on page 20, line 2 (paragraph [0069]) the word "alkynl" was replaced with the word "alkynyl"; on page 7, line 8, page 20, line 8 (paragraph [0017]) and on page 20, line 3 (paragraph [0069]) the word "guanly" was replaced by the word "guanyl"; and on page 17, line 10 (paragraph [0061]) an end-of-sentence period was placed between the words "FGFR" and "More".

Further in addition, Applicant has noticed that the general formula that presents the claimed compounds is somewhat inappropriate. General formulae "Compound I" and "Compound II", according to embodiments of the present invention, represent tyrphostin compounds of the quinoxaline family and the quinazoline family, respectively. It is well known in the art that quinoxalines and quinazolines both have a heteroaryl ring, which is fused with an aryl ring. As is well known in the art and is further defined in the instant application, the terms aryl and heteroaryl describe cyclic groups that have a completely conjugated pi-electron system. As is further well known in the art, such a conjugated pi-electron system can

be schematically described either by a set of conjugated double bonds or by an internal circle which represents the conjugated system. The Formulae presented in the instant application are schematically described such that the fused aryl rings of the tyrphostin compounds include a set of conjugated double bonds to describe aryl ring and an internal circle which represents the conjugated system to describe the heteroaryl ring.

Applicant has chosen to amend, throughout the instant application, the general formulae of Compound I and Compound II, such that the conjugated pi-electron systems of both the aryl ring and the heteroaryl ring are represented by an internal dashed-line circle, replacing two double bonds in the central ring. Specifically, the general formula of Compound I and Compound II was replaced in the Specification on page 6, lines 10-14 ([paragraph 0013]) and on page 19, lines 7-11 (paragraph [0065]), and in the claim 1 and 28. Applicant believes that the general formula of the compounds of the present invention, as amended, is appropriate.

This amendment has no bearings on the scope of the subject matter.

Amendments to the abstract

Applicant has chosen to amend the abstract so as to read on the claimed subject matter and further so as to appropriately present the formula of Compound II, as delineated above.

Amendments to the claims

Applicant has chosen to amend independent claims 1 and 28, as well as claims depending therefrom, so as to read on compounds defined by Compound II, in which the variables A, D and Y are each a nitrogen and variable B is a carbon. As a result, claim 8 has been canceled as reciting limitations now included in amended claim 1.

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35 U.S.C. § 112 Second Paragraph Rejections

The Examiner has rejected claims 1-3, 6-11 and 28-31 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-3, 9 and 28 have been amended.

In one particular (Item a), the Examiner has stated that claims 1, 28 and the claims dependent thereon, are rejected because the limitation "prodrug" has indefinite metes and bounds because it is unclear where the site of functional group for a "prodrug" is. The Examiner further stated that many of the substituents are esters or amide (e.g., carboxy, sulfonamide, etc.) which are typical functional groups for a "prodrug", and thus, it is unclear if additional ester or amide groups are intended.

Applicant wishes to direct the Examiner's attention to page 21, line 14 to page 22, line 6 (paragraph [0075]), where the term "prodrug" is clearly defined:

> *"As used herein in the specification and in the claims section that follows, the term "prodrug" refers to an agent which is converted into an active parent drug in vivo. Prodrugs are often useful because in some instances they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility compared to the parent drug in pharmaceutical compositions. An example, without limitation, of a prodrug would be a compound of the present invention which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is not beneficial, but which then is metabolically hydrolyzed to the carboxylic acid once inside the cell where water solubility is beneficial.".*

Applicant therefore contends that the term "prodrug" also encompasses compounds which are already considered as prodrugs, as is well accepted in the art.

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Notwithstanding the above, Applicant has chosen, in order to expedite prosecution, to amend claims 1 and 28, so as to no longer recite the term "prodrug".

In another particular (Item b), the Examiner has stated that claim 1 is rejected because the definition of R_1 includes the moiety "guanly" which is not an art recognized group, and that it is believed "guanly" is typographical error.

While inspecting the claims, Applicant has found another typographical error similar to that found by the Examiner, where "alkynl" is written instead of "alkynyl". Claim 1 has now been amended to correct these two typographical errors. The same typographical errors were found in claim 28 which is now amended accordingly.

As indicated above, the specification has also been amended so as to correct the same typographical errors.

In another particular (Item c), the Examiner has stated that claim 2 lacks antecedent basis because it depends on claim 1 but recites R_3, R_5 and R_7 (each) as "a pair of electrons" which is not recited in claim 1, and because it is unclear if a double bond is intended, and that claim 3 is rejected as being dependent on claim 2.

In claim 1, R_3, R_5 and R_7 are clearly defined as being selected from a group of substituents which include a pair of electrons (see, in claim 1, line 4 on page 99). Applicant therefore strongly believes that there is a clear antecedent basis for the phrase "a pair of electrons" in claim 1.

The phrase "a pair of electrons" is a commonly used chemical definition of a pair of electrons in the outermost shell of an atom, which is not used in bonding, and which in certain circumstances will allow the atom to bond with other atoms, ions, or molecules that are electrons deficient by providing both of the electrons. This term is typically not used to describe a double bond. Applicant respectfully traverses this rejection.

In another particular (Item d), the Examiner has stated that claim 28 is rejected because it recites the limitation of "enriching" which is unclear if purity is intended or if a different physical forma is intended (e.g., crystalline v. polymorph).

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Applicant wishes to point out in this respect that the instant application teaches processes and products thereof, in which geometrical isomers of tyrphostin compounds are isolated from one another such that in a synthetic preparation, one geometrical isomer is present in excess over its counterpart isomer, namely the preparation is enriched by one particular isomer. The Examiner's attention is kindly directed to page 22, lines 16-19 (paragraph [0078]) of the instant application, where the term "enriched isomer preparation" is defined:

> *"As used herein in the specification and in the claims section that follows, the phrase "enriched isomer preparation" refers to a preparation in which one isomer is represented in a higher proportion as compared to its synthesis proportion".*

It is therefore clear that the term "enriching" is defined as a process of increasing the proportion of one isomer over that of other isomers in a mixture of isomers which are formed simultaneously during the synthetic procedure.

Notwithstanding the above, and in order to more clearly define the claimed subject matter, Applicant has chosen to amend claim 28, so as to recite "***A method of enriching, for a specific isomer, a tyrphostin*** *of a general formula ...".*

Similarly, Applicant has chosen to amend claim 1, so as to recite "***A purified tyrphostin isomer*** *comprising a compound of a general formula ...".*

Consequently, claims 2, 3, 6, 7 and 9 have been amended, so as to be in line with the preamble of claim 1.

In another particular (Item e) the Examiner has stated that claim 30 lacks antecedent basis because it depends on claim 28 but recites R_3, R_5 and R_7 (each) as "a pair of electrons" which is not recited in claim 28, and that it is unclear if a double bond is intended.

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As argued re: *Item c* above, in claim 28, R_3, R_5 and R_7 are clearly defined as being selected from a group of substituents which include a pair of electrons (see, in claim 28, line 9 on page 107).

Applicant believes to have overcome the Examiner's 35 U.S.C. 112, second paragraph rejections.

35 U.S.C. § 112 First Paragraph Rejections

The Examiner has rejected claims 1-3, 6-11 and 28-31 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, and that the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, the Examiner has stated that Compound II does not have description in terms of a generic process of making, bioactivity as well as working examples showing the preferred reagents or reaction condition, and thus, the specification fails to provide written description for compounds of formula II or preparation thereof.

The Examiner's attention is kindly drawn to the specification, and particularly to page 6, line 14 (paragraph [0013]) and page 19, line 11 (paragraph [0065]), where distinct definition under general formula "Compound II" is presented which clearly defines the claimed compounds according to the instant application, and to page 8, line 11 (paragraph [0021]), page 9, lines 11, 14 and 18 (paragraphs [0026], [0027] and [0028]), page 21, line 12 (paragraph [0074]) and page 30, lines 6 and 10 (paragraph [0121] and [0122]), where the process of preparation of the claimed compounds according to the instant application is distinctly presented.

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35 U.S.C. § 102(b) Rejections

The Examiner has rejected claims 1 and 7-9 under 35 U.S.C. 102(b) as being anticipated by Mertens *et al.* (US 4,954,498).

Specifically, the Examiner has stated that in column 4, Mertens *et al.* disclose the compound 7,8-dihydro-1H-imidazo[4,5-g]quinazolin-8-one, a tautomer of Compound II with the following substituents:

R_1, R_2, R_3, R_5 and R_7 each represents hydrogen; and

R_6 is hydroxy at the 8-position;

and that the disclosed compound has pharmaceutical composition, and thus, a preparation thereof is also inherently taught.

The Examiner has also rejected claims 1 and 7-9 under 35 U.S.C. 102(b) as being anticipated by Rewcastle *et al.* (*J. Med. Chem.*, 1996, Vol. 39, pp. 918-928).

Specifically, the Examiner has stated that on page 920, compound 39 is a tautomer of Compound II with the following substituents:

R_1 is an alkyl group;

R_2, R_3, R_5 and R_7 each represents hydrogen;

R_6 is hydroxy at the 8-position.

The Examiner has also rejected claims 1 and 7-9 under 35 U.S.C. 102(b) as being anticipated by Alkhader et al. (*J. Chem. Soc.*, Perkin Trans. 1, Organic & Bio-Org. Chem. (1972-1999), 1979, Vol. 4, pp. 1056-62, or CA 91:123679).

Specifically, the Examiner has stated that on page 1060, compound No. 9, namely 1,2-dimethylimidazo[4,5-g]quinazolin-5-one, is a tautomer of Compound II with the following substituents:

R_1 and R_2 each is an alkyl group;

R_3, R_5 and R_7 each represents hydrogen; and

R_6 is hydroxy at the 8-position.

Applicant contends that the instant application teaches a tyrphostin isomer which is obtained in excess with respect to its counterpart isomer, hence, the instant application teaches purified isomers. The instant application was spun from the

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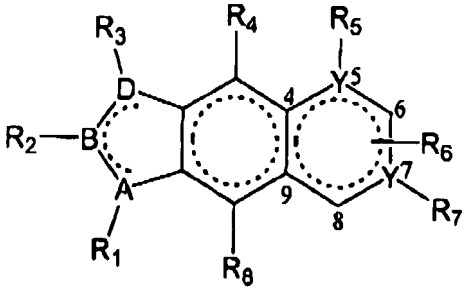
surprising finding that such purification results in the formation of one isomer that is more active then the other isomer and more active than the mixture of both isomers used together.

The compounds taught by the cited art are tautomers of hydroxyls, and hence are α,β-unsaturated carbonyls. It is therefore clear that during the formation of the unsaturated "carbonyl" tautomer stemming from a hydroxyl substituent, it is unlikely that both geometrical isomers will be formed (due to thermodynamic parameters) and hence the compounds taught in the cited references do not stand for a purified isomer, obtained from a mixture of geometrical isomers) but rather stand only for the obtained compounds.

Notwithstanding the above, and in order to expedite prosecution, Applicant has chosen to amend claim 1 so as to read:

"A purified tyrphostin isomer comprising a compound of a general formula:



(Compound II)

wherein,

[...]

R_6 is selected from the group consisting of alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, N-sulfonamido, S-sulfonamido, trihalomethylsulfonamido, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro,

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halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, ureido, guanyl, guanidino, amino and a physiologically acceptable salt thereof;

[...]whereas ***R_6 is at position 6.***"

As a result, claim 6 has been canceled as reciting limitations now included in amended claim 1. Claim 7 has also been canceled.

Applicant strongly believes that since none of the cited references teaches the claimed purified tyrphostin, amended claim 1, as well as claim 8 and 9 are not anticipated by these references and are therefore allowable.

In view of the above amendments and remarks it is respectfully submitted that amended claims 1-3 and 9, claims 10 and 11, amended claim 28, claim 29, amended claim 30 and claims 31 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Date: October 15, 2007

Encl.:

Petition for Extension for Three (3) Months